Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2016, Vol. 32, No. (4):
Pg. 1977-1982

Synthesis and Antimicrobial Activity of Azetidin-2-one Fused 2-Chloro-3-formyl Quinoline Derivatives

GOVIND NAYAK[1]*, BIRENDRA SHRIVASTAVA[1] and AKHLESH KUMAR SINGHAI[2]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur- 302 025, India.
[2]Lakshmi Narain College of Pharmacy, Bhopal- 462 021, India.
Corresponding author E-mail : nayak.govind@rediffmail.com

http://dx.doi.org/10.13005/ojc/320423

(Received: June 13, 2016; Accepted: July 28, 2016)

ABSTRACT

Azetidin-2-one fused 2-chloro-3-formyl quinolines derivatives, 3-chloro-4-(2-chloro-8/7/6-methoxyquinolin-3-yl)-1-(2,4-dinitro/4-nitro phenylamino)azetidin-2-one,3-chloro-4-(2-chloro-8/7/6-chloroquinolin-3-yl)-1-(2,4-dinitro/4-nitro phenylamino)azetidin-2-one, 3-chloro-4-(2-chloro-8/7/6-methylquinolin-3-yl)-1-(2,4-dinitro/4-nitrophenylamino) azetidin-2-one were synthesized by four steps, respectively from N-arylacetamides, 2-chloro-3-formyl quinolines, 2,4-dinitro/4-nitro phenyl hydrazine reflux with chloroacetyl chloride and triethyl amine. However yields of quinolines having electron donating groups in all cases. The structures of the synthesized compounds have been established on the basis of physical and spectral data. The antibacterial and antifungal activity of these compounds was tested by filter paper disc method against *Staphylococcus aureus* (MTCC96), *Escherichia coli* (MTCC722) and *Candida albicans* (MTCC183). The results showed that azetidin-2-one fused 2-chloro-3-formyl quinolines derivatives are better in inhibiting the growth of both types of organisms. Compounds AZT b2, AZT b3 to AZT g2, AZT g3 were found to be more potent compared to standard drug.

Keywords: 2-chloro-3-formyl-quinoline, Vilsmeier-Haack reagent, 2, 4-dinitro/4-nitro phenyl hydrazine, triethyl amine, chloroacetyl chloride, antimicrobial activity.

INTRODUCTION

Substituted quinolines are very simply, efficiently and conveniently synthesized in less time and high yield with less amount of raw material under mild condition with the help of Vilsmeier-Haack reagent ($DMF+POCl_3$) and substituted acetanilide. Quinoline has been posssess a wide spectrum of biological activities.Now a days quinoline derivatives are used for a convenient starting material of various further substituted quinoline.

Formylation of heterocyclic compounds[1], may be achieved by heating heterocyclic compound with Vilsmeier reagent i.e ($DMF+POCl_3$) phosphorous oxychloride and dimethyl formamide, the intermediate is hydrolysed in the presence of mild base give 2-(ortho)-substituted heterocyclic compound[2]. This

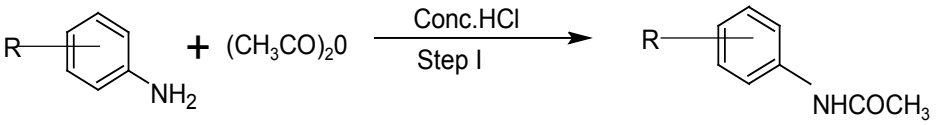
reaction is known as Vilsmeier-Haack reaction. The treatment of infectious diseases still remains an important and challenging problem. The search of novel antimicrobial agents is a field of current and growing interest. Many compounds have been synthesized with this aim; their clinical use has been limited by their relatively high risk of toxicity, bacterial resistance and/or pharmacokinetic deficiencies[3-4]. According to the literature, pyrazoloquinoline and triazolo-thiadiazole quinoline derivatives are reported to possess various biological activities such as antibacterial[5], antifungal[6] anti-inflammatory[7]. As a part of our continuing interest, we have investigated for the first time cyclic azetidin-2-one fused 2-chloro-3-formyl quinoline derivatives with an aryl hydrazine group.

METHODS AND MATERIALS

All chemicals were used of analytical grade from Chemdyes Corporation (Chemco) limited. All melting points were taken in open capillaries tube and are an correct. The progress of all reaction of the synthesized compound was monitored by TLC i.e (Thin layer chromatography). TLC was run using silica gel $PF_{254, 366}$ as an adsorbent and ethyl acetate - n-hexane in different ratio as eluent. Spot were visualized using solid fumes, by keeping of TLC plate in iodine chamber.

REACTION

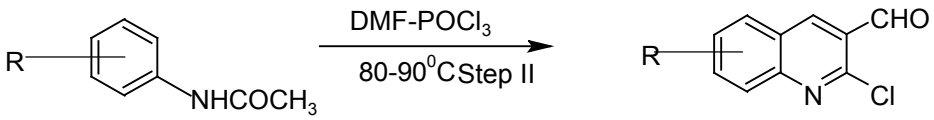
Step I



1 2

Structure 1& 2 R= 2-OCH_3, 3-OCH_3, 4-OCH_3, 2-Cl, 3-Cl, 4-Cl

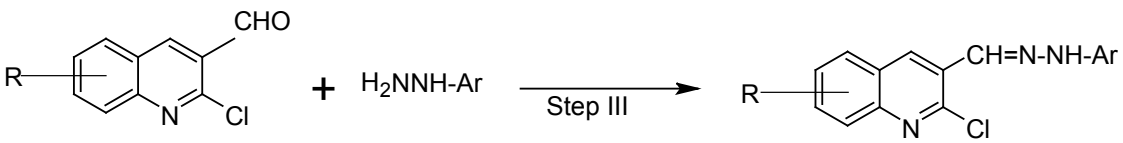
Step II



2 3

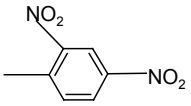
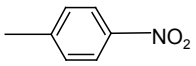
Structure 3 R= 8-OCH_3, 7-OCH_3, 6-OCH3, 8-Cl, 7-Cl, 6-Cl

Step III

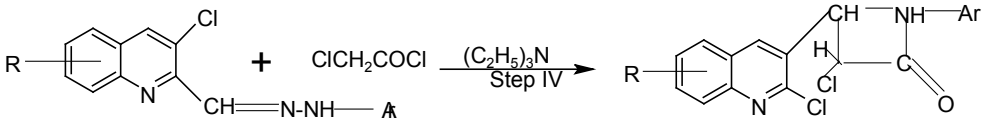


3

4 b2, 4 c2, 4 d2, 4 e2, 4 f2, 4 g2
4 b3, 4 c3, 4 d3, 4 e3, 4 f3, 4 g3

Step III	Ar
4 b2, 4 c2, 4 d2, 4 e2, 4 f2, 4 g2	
4 b3, 4 c3, 4 d3, 4 e3, 4 f3, 4 g3	

Step IV



4 b2, 4 c2, 4 d2, 4 e2, 4 f2, 4 g2
4 b3, 4 c3, 4 d3, 4 e3, 4 f3, 4 g3

AZT b2-AZT g2
AZT b3-AZT g3

Table 1: Physical data of synthesized compounds

S. No.	Code	Molecular formula	Molecular Weight (gm)	Melting point	Percentage yield	R_f value(Ethylacetate : n-hexane)
1.	CFQ	$C_{10}H_6NOCl$	191.616	144-146°C	79	0.67
2.	AZT b2	$C_{19}H_{13}Cl_2N_5O_6$	478.690	264-267°C	74	0.76
3.	AZT b3	$C_{19}H_{14}Cl_2N_4O_4$	434.231	210-214°C	55	0.65
4.	AZT c2	$C_{19}H_{13}Cl_2N_5O_6$	478.690	228-235°C	68	0.69
5.	AZT c3	$C_{19}H_{14}Cl_2N_4O_4$	434.231	186-189°C	61	0.89
6.	AZT d2	$C_{19}H_{13}Cl_2N_5O_6$	478.690	219-225°C	81	0.58
7.	AZT d3	$C_{19}H_{14}Cl_2N_4O_4$	434.231	164-167°C	74	0.68
8	AZT e2	$C_{18}H_{10}Cl_3N_5O_5$	482.321	211-214°C	80	0.89
9	AZT e3	$C_{18}H_{11}Cl_3N_4O_3$	436.542	189-192°C	89	0.75
10	AZT f2	$C_{18}H_{10}Cl_3N_5O_5$	482.321	196-198°C	84	0.72
11	AZT f3	$C_{18}H_{11}Cl_3N_4O_3$	436.542	167-169°C	64	0.61
12	AZT g2	$C_{18}H_{10}Cl_3N_5O_5$	482.321	187-192°C	56	0.97
13	AZT g3	$C_{18}H_{11}Cl_3N_4O_3$	436.542	156-162°C	92	0.79

Experimental Procedure for

IR spectra were recorded on a FT-IR (Bruker) spectrophotometer, ^{1}HNMR Bruker Avance II 400 MHz instrument using DMSO as solvent and TMS as internal reference (Chemical shift in ä, ppm). The following abbreviations were used to indicate the position of functional groups in term of stretching and bending (FT-IR), peak multiplicity s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, dd-doublet of doublet (^{1}HNMR).

Step I Preparation of ortho substituted acetanilide[8, 9]

Aniline (5 ml) is dissolved in hydrochloric acid (4.6 ml concentrated hydrochloric acid and 12.5ml water) in a beaker. To the clear solution are

added acetic anhydride (6.5 ml).The mixture is stirred until acetic anhydride has completely reacted. The mixture are immediately poured in to a solution of sodium acetate (8.3 gm) in water (25 ml).The solution is stirred and cooled in ice. The separated acetanilide is filtered. It is recrystallized from boiling water (100-125 ml) to which ethyl alcohol has been added (Table 1).

Step II Preparation of 2-chloro-3-formyl-quinoline CFQ [8, 9]

To a solution of acetanilide (N-phenylacetamide) (5 mmoles) in dry DMF (15 mmoles) at 0-5°C $POCl_3$ (60 mmoles) was added dropwise with stirring and the mixture was then stirred at 80 – 100°C for time ranging between 4-16 hr. The mixture was poured on to crush ice, stirred for 5 minutes and the resulting solid filtered, washed well with water and dried. The compounds were recrystallized from ethyl acetate. Phosphoryl chloride (commonly called phosphorus oxychloride) is a colorless liquid with the formula $POCl_3$. It hydrolyses in moist air to phosphoric acid to release choking fumes of hydrogen chloride. It is manufactured industrially on a large scale from phosphorus trichloride and oxygen or phosphorus pentoxide. It is mainly used to make phospha (Table 1).

Step III Preparation of 2-chloro-8-methoxy-3-((2, 4-dinitro/4-nitro phenylhydrazono) methyl) quinoline (4b2-4g2 and 4 b3-4 g3)

To a DMF solution of 2-chloro-8-methoxyquinoline-3-carbaldehyde 6 mmoles were added aryl hydrazine (phenyl hydrazine 11 mmoles) and refluxed for three hours, and then left to cool to room temperature or the solvent was removed and the separated solid was poured in to the water. The precipitated product was filtered, washed well with water and dried (Table 1).

Step IV Preparation of 3-chloro–4-(2-chloro–8-methoxyquinolin–3-yl) – 1- (2, 4-dinitro/4-nitro phenylamino)–azetidin–2-one (AZT b2-AZTg2 and AZT b3-AZT g3)

The compound 2-chloro-8-methoxy-3-((2, 4-dinitro/4-nitro phenylhydrazono) methyl) quinoline

Table 2: Antimicrobial activities of Compounds AZT b2-AZT g3 (Diameter of the zone of inhibition in mm)

Compound	Antibacterial activity		Antifungal activity
	***Staphylococcus aureus*(MTCC96)**	***Escherichia coli* (MTCC722)**	***Candida albicans* (MTCC183)**
AZT b2	11	9	10
AZT b3	14	13	8
AZT c2	13	14	11
AZT c3	15	13	9
AZT d2	11	8	9
AZT d3	14	14	12
AZT e2	13	13	10
AZT e3	15	12	9
AZT f2	11	6	7
AZT f3	14	13	11
AZT g2	13	14	8
AZT g3	15	12	10
Standard	18	18	13
*Control	0	0	0

* The solvent (control) is Dimethy formamide

1. *Staphylococcus aureus* reference compound Amikacin
2. *Escherichia coli* reference compound Amikacin
3. *Candida albicans* reference compound Ketoconazole

step-III b1 (0.01 mol) was dissolved in DMF (40ml) and triethylamine (0.02 mol) was added to it. Chloroacetyl chloride (0.02 mol) was added dropwise a period of 30 minutes. The reaction mixture was refluxed for 5 hr, and filtered to separate the solid formed. The filtrate was poured on to crushed ice, the product was filtered and recrystallized from ethylacetate (Table 1).

Characterization data of the synthesized compound[10-11]

Acetanilide: FT-IR cm^{-1} 3295 (N-H), 1664 (CO), 1584 (C=C), ^{1}HNMR (400 MHz, DMSO), δ; 8.72 (s, 1H, NH), 2.1 (s, 3H, CH_3), 7.2 (d, 1H, Ar-H). 2-Chloro-3-formyl quinoline (CFQ): FT-IR cm^{-1} 2896.53 (C – H Str,Ar) 1684.39 (C=O Str) 1574.14 (C=N Str) 1455.03 (C = C Str) 1367.35 (C – N Str,Ar) 749.25 (C – Cl Bending) ^{1}HNMR (400 MHz, DMSO), δ; 10.5 (s, 1H, CHO), 8.8 (s, 1H, H-4), 8.1 (m, 1H, H-6), 7.7 (m, 1H, H-7)

3-chloro–4-(2-chloro–8/7/6-methoxyquinolin–3-yl)-1-(2, 4-dinitro phenylamino) – azetidin - 2 –one (AZT b2, AZT c2, AZT d2): FT-IR cm^{-1} 2998.1(C-H Ar), 3449.10 (N-H Str), 1682.51 (C=O Str), 1139.46 C – N (Str Ar), 758.25 (C – Cl Bending). ^{1}HNMR (400 MHz, DMSO), δ; 12.10 (s, NH) 9.21 (s, 1H, CHO) 7.98 (s, 1H, C4- H) 7.67 (m,CH-5) 3.83 (s, CH_3).

3-chloro–4-(2-chloro–8/7/6-methoxyquinolin–3-yl)-1-(4-nitro phenylamino) – azetidin - 2 – one (AZT b3, AZT c3, AZT d3): FT-IR cm^{-1} 3262.86 (N– H Str, Ar) 1696.94 (C=O Str) 1566.45 (C=N Str) 1592.64 (N-H bending in amide) 1052.68 (CH_3O Str). ^{1}HNMR (400 MHz, DMSO), δ; 7.82 – 8.01 (m, Ar-H) 10.37 (s, 1H, CH heteroaromatic proton) 8.43 (s, 1H, H-4) 7.79 (d, C=O) 4.1 (d, 1H CH-Cl) 3.35 (s, 3H, OCH_3) 7.32 (d, 1H, H-5).

3-chloro-4-(2,8/7/6-dichloroquinolin-3-yl)-1-(2, 4-dinitro phenylamino) azetidin-2-one (AZT e2, AZT f2, AZT g2): FT-IR cm^{-1} 3487.00 (C – H Str, Ar) 3306.34 (N-H Str) 1748.36 (C=O Str) 1519.21 (C = N Str) 1335.03 (C – N Str, Ar) 1060.31 (CH_3O, Str) 794.11 (C – Cl, Str) 722.06 (C – Cl Bending). ^{1}HNMR (400 MHz, DMSO), δ; 7.31 – 8.17 (m,Ar-H) 10.16 (s, 1H, CH Heteroaromatic proton) 8.78 (s, 1H, H-4) 8.34 (m, 1H, H-8) 7.28 (C=O group d, 1H) 3.17 (m, CH-N aromatic)

3-chloro-4-(2, 8/7/6-dichloroquinolin-3-yl)-1-(4-nitro phenylamino) azetidin-2-one (AZT e3, AZT f3, AZT g3): FT-IR cm^{-1} 3362.55 (C – H Str, Ar) 1681.83 (C=O Str) 1531.60 (C = N Str) 1418.67 (C – N Str, Ar) 776.88 (C – Cl, Bending). ^{1}HNMR (400 MHz, DMSO), δ; 7.40 – 8.01 (m,Ar-H) 10.24 (s, 1H, CH Heteroaromatic proton) 8.03 (s, 1H, H-4) 7.50 (m, 1H, H-7) 6.58 (C=O, d, 1H).

Antimicrobial activity[12-18]

The compounds AZT b2 - AZT g3 were tested for their antibacterial activity and antifungal activity by filter paper disc method using nutrient broth medium (contained g/L: beef extract 30gm; Casein hydrolysate 17.5 gm; soluble starch 1.5gm; pH 7.4). The Gram-positive and Gram-negative bacteria utilized in this study consisted of *Staphylococcus aureus*, *Escherichia coli* and fungi *Candida albicans*. In the filter paper disc method, sterile paper discs (05mm) impregnated with compound dissolved in DMF (Dimethyl formamide) at concentration 200µg/mL were used. Then, the paper disc impregnated with the solution of the compound tested was placed on the surface of the media inoculated with the microorganism. The plates were incubated at 37°C for sufficient period of time. After incubation were noted and the results are given in Table 2.

RESULTS AND DISCUSSION

All the synthesized compounds were confirmed by their spectral data (Table 1) and the screened for anti-bacterial against Staphylococcus aureus, Escherichia coli and ant-fungal activity against Candida albicans, compounds (AZT b2-AZT g2) showed moderate to good antibacterial and antfungal activity (Table 2) when compared to that of reference Amikacin and Ketoconazole respectively. The structures of all compounds were confirmed by FT-IR and ^{1}H NMR spectra (2.3 sections). The FT-IR spectra of the azetidine fused 2-chloro-3-formyl quinoline derivatives AZT b2 –AZT g2 showed absorption bands at about 1748-1708 cm^{-1} characteristic for C=O stretching vibration, 1528-1519 cm^{-1} for C=N Stretching

associated with quinoline 2927 cm^{-1} for C-H aromatic stretching, 759 cm^{-1} absorption for C-Cl stretching, absorption band at 3306.34 cm^{-1} for N-N=C vibration provided confirmatory evidence for ring closure. Further support was obtained from the ^{1}HNMR spectra, resonance assigned 10.6 δ (s, 1H, CHO), 8.5 δ (s,1H, H-4), 2.6 δ (s, 3H, CH_3) for 6-methyl/7-methyl/8-methyl (2.8 δ, s,3H), 4.0 δ (s, 3H, OCH_3) for 6-methoxy/7-methoxy/8-methoxy, 10.7 (s, 1H, CHO), 8.5 (s, 1H, H-4), 7.7 (m, 1H, H-5), 7.5 (s, 1H, H-8), 7.2(m, 1H, H-6), 10.8 (s, 1H, CHO), 8.6 (s, 1H, H-4), 8.1 (m, 1H, H-8), 7.7 (m, 1H, H-7), 7.6 (s, 1H, H-5) for the confirmation of the compounds. Having obtained chloro and formyl group substituted quinolines the possible transformations of these functionalities could afford the new quinolines (AZT b2-AZT g2), which are equally important synthon for the synthesis of fused quinoline systems.

ACKNOWLEDGEMENTS

The authors are grateful to the LNCP, Bhopal for providing the necessary facilities to carry out this research work, and also thankful to the SAIF Lab, Panjab university, Chandigarh for recording the spectral data of the compounds.

REFERENCES

1. Meth, C.O.; Narine B. *tetrahedron let.,* **1978**,*19,* 2045-2048.
2. Meth, C.O.; Narine B.; Tarnowski B. *J. Chem. Soc; perkin Trans-1*, **1981**, 1520-1530.
3. Pett, K. R.; Cage D. G.; Liebman A. J. *Int. J. Antimicrobial Agents*, **2000**, *15,* 299.
4. Savage, P. B. *Eur. J. Org. Chem.*, **2002**, *5,* 759.
5. Hirosato, K.; Fumino S.; Kiyotaka K.; Goro T. *J. Med. Chem.*, **1998**, *31*, 221.
6. Pramilla, S. *Indian J. Heterocyclic Chem.*, **1998**, *10*, 13.
7. Gupta, R. K.; Gupta A.; Kachroo P. L. *Indian J. Chem.*, **1998**, *37B*, 1211.
8. Srivastava, A.; Singh R. M. *Indian J.Chem.,* **2005**, *44B,* 1868-1875.
9. John, R. D.; Applications of Absorption Spectroscopy of Organic Compounds, Prentice Hall of India (P): New Delhi **1969**, 33-38.
10. Silverstein, R.M.; Webster F. X.; Spectrometric Identification of Organic Compounds, John Wiley and Sons: Inc.**1998**.
11. McLafferty, F. W.; Interpretation of Mass Spectra, W.A. Benjamin Inc. publishers: New York **1974**.
12. Holt, J.G.; Krieg N.R.; Sneath, P.H.; Stanley, J.T.; Williams, S.T.; Bergy's Manual of Determinative Bacteriology, Williams and Wilkins: Baltimore **1996**, 324.
13. Chung, K.C.; Goepfert J.M. *J. Food. Sci.*, **1970***, 35*, 326-328.
14. Ferreira, M.A.; Lund, B.M. *Appl. Microbiology*, **1987**, *5,* 67-70.
15. Glynn, H. J.; Heinke G.W.; Environmental Science and Engineering Microbiology and Epidemiology**,** Prentice Hall International: New Jersey **1996**, 266.
16. Pelczar, M. J.; Chan E.C.S.; Krieg N.R.; Microbiology, McGraw-Hill Book Company: New York **1986**, *333*, 435.
17. Rex, J.H.; Walsh T.J.; Sobel J.D. *Clin. Infect. Dis.*, **2000**, *30*, 662-678.
18. Pfaller, M. A.; Diekema, D. J.; Jones R. N. *J. Clin. Microbiology*, **2001**, *39*, 3254 – 3259.